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10/502,180	07/21/2004	Romulus Kimbro Brazzell	OP/4-32328A	3995

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ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
HUANG, GIGI GEORGIANA	

ART UNIT	PAPER NUMBER
1612	

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12/10/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/502,180	BRAZZELL ET AL.	
	Examiner	Art Unit	
	GIGI HUANG	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-20* is/are pending in the application.

4a) Of the above claim(s) *15-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/21/2004, 11/8/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I in the reply filed on July 16, 2008 is acknowledged. Applicant has also elected age-related macular degeneration as the angiogenesis-mediated ocular disorder for the examination. As Applicant did not distinctly and specifically point out the supposed errors in the election requirement, the election has been treated as an election without traverse. Upon examination, the angiogenesis-mediated ocular disorder is expanded to glaucoma.

Status of Application

2. Applicant has elected Group I in response to restriction requirement and elected the species age-related macular degeneration as the angiogenesis-mediated ocular disorder for the examination. Upon examination, the angiogenesis -mediated ocular disorder is expanded to glaucoma.

Due to restriction, based on election of Group I, claims 15-20 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

3. Claims 9-14 are present for examination at this time.

Specification

4. The disclosure is objected to because of the following informalities: The term : "neovascularisation" is misspelled. The correct spelling is "neovascularization".

Appropriate correction is required.

Claim Objections

5. Claims 11 is objected to because of the following informalities: "neovascularisation" is misspelled. The correct spelling is "neovascularization". Appropriate correction is required.

Information Disclosure Statement

6. The information disclosure statement filed 11/8/2004 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The foreign references do not have copies presented and it has been placed in the application file, but the information referred to therein has not been considered.

It is noted that the Moser et al. reference is not in the prior art. However, a copy is included in the action and has been considered.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 9-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. In the instant case, the claims are to the compounds of formula I as addressed by claim 9, a pharmaceutically acceptable salt, or a prodrug ester thereof.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The specification must provide adequate written description to identify the genus of the claim. The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163.

In the instant case, there are no structures, compounds, formulations, or examples described in the specification for prodrugs nor which forms, methods, or points of substitution or what type of substitutions of the genus would be readily cleaved in vivo to liberate the remaining portion of the compound. A "prodrug" is not adequately defined or enabled. Applicants provided no guidance as how the compounds are made more active in vivo or what was envisioned as at the time of the invention to be a "prodrug" without guidance, has as the broadest reasonable interpretation is any possible substituent that would form the cleaved group (e.g. a phenyl group, a heterocycle, multiple substituted heterocycle, sulfonyl group, a methyl group) and any point of the genus as no location of attachment is disclosed, which quickly expands beyond what is represented by the written compound of the instant claims. As a result, the specification does not provide for what the inventors were in possession of at the time of filing. The choice of a possible "prodrug" will also vary from drug to drug. Therefore, more than minimal routine experimentation would be required to determine which ester will be suitable for the instant invention. The application does not provide any guidance for one skilled in the art to determine what moieties the Applicant was in possession of at the time of the invention. Additionally, the examples presented do not present any prodrug forms and recite a "5-methyl-2-(2'-chloro-6'-fluoroanilino) phenylacetic acid drug substance" which does not present a prodrug form not what the component actually is.

Applicants provide no reasonable assurance that any and all prodrugs will have the ability to regenerate in vivo to the instant compounds by one or more biological

processes. This is evidenced by the specific compound assay for receptor binding whereby many did not have adequate binding and those compound that did bind have to be evaluated to ascertain if there is to be any adequate and measurable amount of activity. As a result, it is not the norm that one can predict with any degree of accuracy a particular prodrug form of an active compound will be more soluble, more easily handled in formulations or be more bioavailable without actual testing in vivo.

Many functional groups (e.g. hydroxy, amino groups) present in drugs are capable at least in theory to being derivatized but determining what is an in vivo hydrolysable ester (and what is not) requires knowledge of an intended effect (i.e. modification of an undesirable property in the parent drug- poor solubility, poor bioavailability, poor shelf-life) which is never identified by the specification. Additionally, the disclosure does not provide adequate description as to what characteristics are required to be a suitable prodrug, such as what would be a sufficient degree of hydrolysis (e.g. 95%? 100?) by which substituent as which point of attachment.

It is unquestionable that claims for prodrugs are broad and generic, with respect to all possible compounds encompassed by the claims. The possible structural variations are limitless. Although the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds even among those compounds specifically disclosed in the examples in the specification. Moreover, the specification lacks sufficient variety of species to reflect this variance in the genus. The specification additionally discloses that not all the compounds formulated were able to bind

adequately to the receptor, and no specific correlation between the binding, function, or structure of the compounds were presented. The specification does not provide sufficient descriptive support for the myriad of compounds embraced by the claims.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the entire scope of the claimed invention.

10. Claims 9-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for free base and salt forms, does not reasonably provide enablement for prodrug forms. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. There is no process enabling such a scope in the specification. The scope of prodrug is nonlimiting as it is not even described what type is suitable to practice the invention much less how to make and use a representative class. Applicants provide no reasonable assurance which if any prodrugs will have the ability to regenerate in vivo to the instant compounds by one or more biological processes. It is not the norm that one can predict with any degree of accuracy a particular prodrug form of an active compound will be more soluble, more easily handled in formulations or more bioavailable without actual testing in vivo.

Pursuant to In re Wands, 8 USPQ2d 1400, factors such as:

(1) The nature of the invention and (2) the breadth of the claims:

The claim is drawn to the compound of formula (I) wherein R is methyl or ethyl; R1 is chloro or fluoro; R2 is hydrogen or fluoro; R3 is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy; R4 is hydrogen or fluoro; and R5 is chloro, fluoro, trifluoromethyl or methyl, a pharmaceutically acceptable salt, or a prodrug ester thereof, as described in claim 9. The specification, while enabling for free base and salt forms, it does not reasonably provide enablement for prodrug forms. The breadth of the claims results in a scope of compounds that is easily in the millions.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

The state of the prior art addresses that formations of prodrugs are difficult, unpredictable, and variable. With regard to predictability, note Burger, provided with this action which emphasizes the many experimental factors for consideration for a successful prodrug as well as the difficulty in extrapolating data from one species to another. See p.976. Also, see Banker provided with this action, who in the first sentence of the 3rd paragraph on p.596 states that "extensive development must be undertaken to find the correct chemical modification for a specific drug." Additionally, Testa which is provided in the action, states the challenge of the biological variety results not just from the "huge number and evolutionary diversity of enzymes" involved in metabolism which may "render prodrug optimization difficult to predict and achieve" (Page 2098, Challenges in prodrug research). Thereby resulting in high unpredictability in the art.

(5) The relative skill of those in the art:

The degree of skill in the art is high.

6) direction or guidance:

None is seen in the specification. Many functional groups (e.g. hydroxy, amino groups) present in drugs are capable at least in theory to being derivatized but determining what is a prodrug (and what is not) requires knowledge of an intended effect (i.e. modification of an undesirable property in the parent drug- poor solubility, poor bioavailability, poor shelf-life) which is never identified by the specification.;

7) presence or absence of working examples:

There is no example of a prodrug in the present case which does not allow one to ascertain the entirely of the claimed genus, the scope, nor how to make the genus claimed;

8) quantity of experimentation needed:

The amount of experimentation to make or use the invention must be considered to determine if undue experimentation is present. With regard to quantity of experimentation needed, note Burger, provided with this action which emphasizes the many experimental factors for consideration for a successful prodrug as well as the difficulty in extrapolating data from one species to another. See p.976. Also, see Banker provided with this action, who in the first sentence of the 3rd paragraph on p.596 states that "extensive development must be undertaken to find the correct chemical modification for a specific drug." Additionally, Testa which is provided in the action, states the challenge of the biological variety results not just from the "huge number and evolutionary diversity of enzymes" involved in metabolism which may "render prodrug optimization difficult to predict and achieve" (Page 2098, challenges in prodrug

research). In view of all these factors undue experimentation would be required to practice the invention.

11. Claims 9-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of corneal graft rejection, ocular neovascularization, neovascularization following injury or infection, choroidal neovascularization (CMV), retinal neovascularization, retrolental fibroplasias, neovascular glaucoma, age-related macular degeneration, diabetic retinopathy, pathologic myopia, ocular histoplasmosis, retinopathy of prematurity, the after effects of corneal transplantation, postsurgical ocular inflammation (e.g. after cataract surgery), cystoid macular edema (CME), retinitis, conjunctivitis, uveitis, ocular photophobia, and herpes keratitis, it does not reasonably provide enablement for treatment and prevention of all angiogenesis-mediated ocular disorders, or the prevention of corneal graft rejection, ocular neovascularization, neovascularization following injury or infection, choroidal neovascularization (CMV), retinal neovascularization, retrolental fibroplasias, neovascular glaucoma, age-related macular degeneration, diabetic retinopathy, pathologic myopia, ocular histoplasmosis, retinopathy of prematurity, the after effects of corneal transplantation, postsurgical ocular inflammation (e.g. after cataract surgery), cystoid macular edema (CME), retinitis, conjunctivitis, uveitis, ocular photophobia, and herpes keratitis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicant have reasonably demonstrated/disclosed that the claimed compound is useful as a therapeutic agent for treating corneal graft rejection, ocular neovascularization, neovascularization following injury or infection, choroidal neovascularization (CMV), retinal neovascularization, retrolental fibroplasias, neovascular glaucoma, age-related macular degeneration, diabetic retinopathy, pathologic myopia, ocular histoplasmosis, retinopathy of prematurity, the after effects of corneal transplantation, postsurgical ocular inflammation (e.g. after cataract surgery), cystoid macular edema (CME), retinitis, conjunctivitis, uveitis, ocular photophobia, and herpes keratitis and/or reducing the risk thereof. However, the claims also encompass using the claimed compound to prevent all antiogenic-mediated ocular disorders which is clearly beyond the scope of the instantly disclosed/claimed invention. Please note that the term "prevent" is an absolute definition which means to stop from occurring and, thus, requires a higher standard for enablement than does "therapeutic" or "treat", especially since it is notoriously well accepted in the medical art that the vast majority of afflictions/disorders suffered by mankind cannot be totally prevented with current therapies (other than certain vaccination regimes) – including preventing such disorders as ocular melanoma or Age-related Macular Degeneration, which are clearly not recognized in the medical art as being a totally preventable condition.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention.

"Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to the prevention and treatment of an angiogenic-mediated ocular diseases by administering a compound of the formula in claim 9. Thus, the claims taken together with the specification imply that all angiogenic-mediated ocular diseases are preventable and treatable by administering a compound of the formula in claim 9.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

Mayo Clinic (Mayo Clinic sheets) states that the cause of ocular melanoma is not know. The standard therapy depending on the size of the tumor is primarily surgical removal and in the case of larger tumors, the only option is removal of the eye. There is no current conventional pharmaceutical treatment for the condition especially for larger tumors, or method of prevention.

Schmidt-Erfurth (Management of neovascular age-related macular degeneration) addresses Age-related Macular Degeneration and how only recently gaining new insights in the pathogenesis of the disease are allowing for improved

treatment for the *management* of the disease, not *prevention* as the etiology is still not clear for those skilled in the art.

(5) The relative skill of those in the art:

The relative skill is high.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for the delivery of the compounds of claim 9 for the following conditions: corneal graft rejection, ocular neovascularization, neovascularization following injury or infection, choroidal neovascularization (CMV), retinal neovascularization, retrolental fibroplasias, neovascular glaucoma, age-related macular degeneration, diabetic retinopathy, pathologic myopia, ocular histoplasmosis, retinopathy of prematurity, the after effects of corneal transplantation, postsurgical ocular inflammation (e.g. after cataract surgery), cystoid macular edema (CME), retinitis, conjunctivitis, uveitis, ocular photophobia, and herpes keratitis. However, the specification does not provide for prevention of every angiogenic-mediated ocular condition including corneal graft rejection, ocular neovascularization, neovascularization following injury or infection, choroidal neovascularization (CMV), retinal neovascularization, retrolental fibroplasias, neovascular glaucoma, age-related macular degeneration, diabetic retinopathy, pathologic myopia, ocular histoplasmosis, retinopathy of prematurity, the after effects of corneal transplantation, postsurgical

ocular inflammation (e.g. after cataract surgery), cystoid macular edema (CME), retinitis, conjunctivitis, uveitis, ocular photophobia, and herpes keratitis.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to prevention of all ocular conditions and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

13. Claims 9-15 are rejected under 35 U.S.C. 102(e) as being anticipated by Ewing et al. (U.S. Pat. Pub. 2003/0143271).

Ewing et al. teaches the use of compositions comprising a coxib component for treating COX-2 mediated disorders. The coxib components include 5-alkyl-2-arylaminophenyl-acetic acid and derivatives thereof. The specific compound cited to be useful in this class is 5-methyl-2-(2-chloro-6-fluoroanilino-)phenylacetic acid and pharmaceutically acceptable salts thereof. It is one of seven specific compounds stated

to be useful in the treatment of COX-2 mediated disorders. The disorders include ophthalmic disorders such as uveitis (inflammation) keratoconjunctivits, diabetic retinopathy, Ocular photophobia, acute trauma (including post surgical), macular degeneration, neovascular glaucoma, and ocular pain. Administration of the composition is oral but topical administration would be immediately envisioned as several of the conditions taught are ophthalmic and direct administration to the eye affected would be immediately be envisioned for effective and direct treatment by one in the art (Abstract, Paragraph 22-23, 39, 41, 80-81, 84, Claim 5).

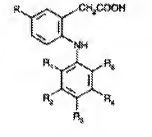
All the critical elements are taught by the cited reference and thus the claims are anticipated.

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 9-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Fujimoto et al. (WO 99/11605).

Fujimoto et al. teaches the use of compositions comprising compounds of the following formula:



(I)

wherein R is methyl or ethyl; R1 is chloro or fluoro; R2 is hydrogen or fluoro; R3 is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy; R4 is hydrogen or fluoro; and R5 is chloro, fluoro, trifluoromethyl or methyl, a pharmaceutically acceptable salt, or a prodrug ester thereof, which is identical to the compounds of instant claim 9 (Abstract, Page 2-3, Claim 1, 3). Fujimoto also teaches the particular embodiment 5-methyl-2-(2-chloro-6-fluoroanilino-)phenylacetic acid (Page 3, 21-example 6). Fujimoto teaches that these compounds are selective cyclooxygenase inhibitors (COX-2 inhibitors) and are particularly useful for the treatment of cyclooxygenase dependent disorders and are useful in ocular applications (Claim 1, 34, 6-8). The applications include treatment of ocular disorders such as ocular inflammation, ocular pain including pain associated with ocular surgery, allergy, photophobia, elevated intraocular pressure (glaucoma), and dry eye disease (Page 4-6, 21). The compounds can be in the form of salts and the compositions taught can be in forms suitable for oral, transdermal, topical, rectal, and parenteral administration (Page 18-20).

All the critical elements are taught by the cited reference and thus the claims are anticipated.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claim 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fujimoto et al. (WO 99/11605) as applied to claim 9-13 above, and in view of Nadkarni et al. (U.S. Pat. Publication 2002/0013357).

The teachings of Fujimoto et al. are addressed above.

Fujimoto et al. do not expressly teach treatment of age-related macular degeneration.

Nadkarni et al. teaches treatment of COX-2 mediated disorders with COX-2 selective inhibitors and that COX-2 mediated disorders include ophthalmic diseases such as ocular photophobia, neovascular glaucoma, corneal graft rejection, ocular neovascularization, conjunctivitis (ocular inflammation), uveitis (ocular inflammation and allergy), diabetic retinopathy, and macular degeneration,.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use the COX-2 selective inhibitor compounds to treat related conditions such as age-related macular degeneration, as suggested by Nadkarni, and produce the instant invention. It would have been obvious for one of skill in the art to use the compounds which are taught to be selective COX-2 inhibitors useful for conditions such as ocular inflammation, allergy, photophobia, and glaucoma which are known to be angiogenesis-related disorders and COX-2 mediated as taught by Nadkarni, to use the compounds for other angiogenesis-related and COX-2 mediated ophthalmic disorders including macular degeneration and diabetic retinopathy as taught by Nadkarni (Paragraph 40, 45, 51).

One of ordinary skill in the art would have been motivated to do this because it is desirable to treat related conditions mediated by the same pathway with the same drugs.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

18. Claims 9-14 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GIGI HUANG whose telephone number is (571)272-9073. The examiner can normally be reached on Monday-Thursday 8:30AM-6:00PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fredrick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

GH
/Zohreh A Fay/
Primary Examiner, Art Unit 1612